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EARLY ONSET OF ADRENAL INSUFFICIENCY IS ASSOCIATED WITH WORSE OUTCOMES

Raghavendra Rao M.V[1], Jerryson Ameworgbe Gidisu[2], Frank Takyi Appiah[3], Ernest Asiamah[4], Hitesh Lakshmi Billa[5], Vijay Kumar Chennamchetty[6], G. Mary Sowjanya[7], Aruna Kumari.B[8], Mubasheer Ali[9]

[1]Department of Medicine, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India.

[2]President and council chairman, Department of Cardiothoracic Surgery, School of Medicine, Kings and Queens Medical College, Ghana, West Africa.

[3]Department of orthopaedic surgery, School of Medicine, Kings and Queens Medical college, Ghana, West Africa.

[4]Department of Histology and embryology, School of Medicine, Kings and Queens Medical college, Ghana, West Africa.

[5]Senior resident, Department of Pulmonology, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India.

[6]Department of Pulmonary Medicine, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India.

[7]Department of Forensic Science, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India.

[8]Department of Respiratory Medicine, ESIC Medical college, Sanath Nagar, Hyderabad, TS, India.

[9]Consultant, MD Internal Medicine, Apollo Hospitals and Apollo Tele Health Services, Associate Professor Department of General Medicine, Shad an Medical College, India.

ABSTRACT

Tuberculosis is adopted to be a critical action of Addison's disease and acute adrenal failure worldwide.Addison's disease is rare but serious adrenal gland disarray. As a result, the adrenal gland can't process cortisol and aldosterone hormones. Thomas Addison was the first to describe Addison's disease in 1855. He showed that tuberculosis (TB) destroyed the bilateral adrenal glands in six cases. Mycobacterium tuberculosis infection is the most common cause of adrenal failure in those with adrenal TB. Bilateral adrenal glands are more commonly affected by adrenal tuberculosis than unilateral glands. Patients with Primary Adrenal Insufficiency due to Adrenal TB require lifelong replacement of Glucocorticoids and Mineralocorticoids. Tuberculosis (TB) is the leading cause of adrenal insufficiency in resource-limited settings. Adrenal infections are an important but under-recognized clinical entity.Differentiating between tuberculosis Addison's disease and other types of adrenal insufficiency can be done with a computed tomography (CT) scan or magnetic resonance imaging (MRI).

Keywords: Primary Adrenal Insufficiency, Adrenal Tuberculosis, Mineralocorticoids, Kanamycin, Amikacin, and Capreomycin.

INTRODUCTION:

Functional adrenal insufficiency, subnormal corticosteroid production during acute illness, results in high morbidity and mortality in critically ill patients (1)

Human immunodeficiency virus (HIV) and TB co-infection may compromise adrenocortical function and produce significant adrenocortical insufficiency (2)

The World Health Organization (WHO) estimates that 190,000 people died of multi drug-resistant tuberculosis (MDR-TB) in 2017 (3)

In Uganda, a high TB-HIV burden country, prevalence of MDR-TB was 1.6% among newly diagnosed patients and 12.0% among previously treated patients in 2017 (4)

HIV infection did not confer an additional risk of adrenal insufficiency among tuberculosis patients in a study of patients in Kenya (5)

Although autoimmune destruction represents the primary cause of adrenal dysfunction in developed countries (80—90%), infectious etiologies represent the major cause of Addison's disease in the developing world, with Mycobacterium tuberculosis being the most common causative agent(6)

In Uganda, a high TB-HIV burden country, prevalence of MDR-TB was 1.6% among newly diagnosed patients and 12.0% among previously treated patients (7)

Adrenocortical dysfunction is a known comorbidity of MDR-TB (8)

Disadvantage of microscopy is that it cannot differentiate between live and dead bacilli and hence cannot be used as a follow-up diagnostic test (9)

Second-line injectable drugs—kanamycin, amikacin, and capreomycin and are recommended to guide multidrug-resistant (MDR) TB treatment initiation.(10)

WHO has published guidance on the role of sequencing for detecting mutations associated with drug resistance in TB (11)

Point-of-care strips for LAM are available on the market for use among the HIV-infected individuals. Importantly, the only approved antibody test for TB is the Alere LAM (12)

The various incidence rates of extrapulmonary TB reported in various studies. The various organs involved in extrapulmonary TB, as reported by various researchers, (13)

TB is the 9th leading cause of mortality globally and Africa alone accounts for about 25% of the mortality (14)

It further stresses the barely adequate health-care delivery services available in sub-Saharan Africa. Due to poor reporting and less robust diagnostic facilities, estimates of the burden of TB in sub-Saharan Africa may not be accurate.(15)

illustrates how the estimated incidence of TB in the World Health Organization (WHO) Africa region compares with other WHO regions (16)

The figure shows that apart from the South-East Asia region, the estimated incidence of TB is higher than the incidences in other regions combined. Nigeria has the highest estimated incidence of TB in Africa (17)

Rarely, adrenal crisis has been precipitated by the administration of rifampin . There is no consensus on adjunctive treatment with corticosteroids (18)

First, hematogenous spread of M. tuberculosis from the lungs to the adrenal glands can cause bilateral destruction of the adrenal glands. Rifampicin, which is part of the backbone of anti-TB therapy can accelerate the hepatic metabolism of glucocorticoids(19)

Tuberculosis may lead to adrenal insufficiency by direct glandular involvement, by extra-adrenal infection, or as a by-product of antituberculous therapy.(20)

HISTORY:
Addison's disease is named after Thomas Addison, who first described the condition in On the Constitutional and Local Effects of Disease of the Suprarenal Capsules (1855).

SYMPTOMS:
Addisonian crisis characterised by low blood pressure. Symptoms tend to be non-specific and include fatigue, nausea, darkening of the skin and dizziness upon standing. Symptoms of Adrenal TB include weakness, tiredness, anorexia, vomiting, diarrhea, abdominal discomfort, Abnormal menstrual periods, dehydration, myalgia, arthralgia, postural disorientation, salt cravings, headache, depression, and memory impairment, dizziness and stomach pain, skin folds, scars on skin, unexpected weight loss.

Hyperpigmentation Addison's Disease:
Addison disease is generally seen with hyperpigmentation due to ACTH melanogenesis. Intraorally pigmentation over the gingival, vermillion border of lip, buccal mucosa, palate tongue, is evident and perceived as first sign.

Addison's crisis:
Many endocrine glands, including the brain, pituitary, thyroid, and adrenals, can be affected by tuberculosis. In developing nations, tuberculous Addison's disease is still a common cause of primary adrenocortical insufficiency. Mycobacterium tuberculosis complex distributes hematogenously to the adrenal glands. In an autopsy series, adrenal involvement was observed in 6% of patients with active tuberculosis. Bilateral adrenal enlargement is seen in the majority of individuals with active or recently acquired disease (less than 2 years), whereas calcification and atrophy are seen in patients with more distant infection or inactive disease. Patients may have Addisonian crisis, that can be fatal, if more than 90% of the cortex has been damaged.

Based on the none of presenting symptoms, diagnosing AD can be difficult. When the main complaints are merely loss of weight and gastrointestinal issues, AD will not be high on the differential diagnostic list. Because of the potential of an adrenal crisis, it is critical to recognise the illness as soon as possible. (21)

This consumption has since receded to the background of ailments that afflict the Western world and today is generally considered a disease of immigrants from endemic areas, the immunocompromised or the destitute. In the developing world, however, tuberculosis continues to account for about 20–30% of cases of Addison's disease (22)

The clinical presentation of primary adrenal insufficiency is protean, and an underlying infectious etiology can further obscure the manifestations. The most frequent manifestations are weakness, fatigue, anorexia, weight loss, nausea, vomiting, hypotension, and skin hyperpigmentation (present in 60– 100% of patients (23,24)

Adrenal TB:
Addison disease is a relatively rare condition, which can have devastating consequences if not promptly recognized and appropriately treated. Often the insidious nature of the disease results in a delay in diagnosis in patients who are not recognized until an acute adrenal crisis develops. Improving inter-professional team members' awareness of this condition will improve outcomes for patients who have Addison disease.

Thomas Addison was the first to describe Addison's disease in 1855. He showed that tuberculosis (TB) destroyed the bilateral adrenal glands in six cases. Mycobacterium tuberculosis infection is the most common cause of adrenal failure in those with adrenal TB. Bilateral adrenal glands are more commonly affected by adrenal tuberculosis than unilateral glands. Differentiating between tuberculous Addison's disease and other types of adrenal insufficiency can be done with a computed tomography (CT) scan or magnetic resonance imaging (MRI).

Many endocrine glands, including the brain, pituitary, thyroid, and adrenals, can be affected by tuberculosis. The adrenal gland is the most usually affected endocrine organ in tuberculosis. Tuberculosis can affect the adrenal glands directly or indirectly. In developing nations, tuberculous Addison's disease is still a common cause of primary adrenocortical insufficiency. Mycobacterium tuberculosis complex distributes hematogenously to the adrenal glands. Asymptomatic infection is not rare, and clinical signs can take years to appear. In an autopsy series, adrenal involvement was observed in 6% of patients with active tuberculosis. Bilateral adrenal enlargement is seen in the majority of individuals with active or recently acquired disease (less than 2 years), whereas calcification and atrophy are seen in patients with more distant infection or inactive disease.

Symptoms of adrenal TB:
Symptoms of Adrenal TB include weakness, tiredness, anorexia, nausea, vomiting, abdominal discomfort, myalgia, arthralgia, postural disorientation, salt cravings, headache, depression, and memory impairment.Fatigue and stomach pain are common symptoms of adrenal insufficiency.Patients may have Addisonian crisis, that can be fatal, if more than 90% of the cortex has been damaged. Based on the non of presenting symptoms, diagnosing AD can be difficult. When the main complaints are merely loss of weight and gastrointestinal issues, AD will not be high on the differential diagnostic list. Because of the potential of an adrenal crisis, it is critical to recognise the illness as soon as possible.

AUTOPSY:
Adrenal tuberculosis is difficult to diagnose due to non-specific symptoms and Unexpected death due to adrenal insufficiency is rare.Adrenal insufficiency (AD) presents a challenge for patients, their physicians and researchers (25)

Tuberculosis being the most common cause of adrenal insufficiency in the developing countries (26)

Sudden deaths due to adrenal diseases are rare and extremely difficult to recognize clinically often discovered at autopsy.

Adrenal insufficiency occurs most commonly in persons who were being treated for critical conditions which led to corticoadrenal function impairment. Adrenal insufficiency remain clinically silent until abrupt adrenal decompensation occurs and sudden death occurs. > 90% of the adrenal cortex bilaterally must be nonfunctional before clinical manifestation of infective, inflammatory, or neoplastic processes occurs causing sudden death.

Both Addison's disease and secondary hypocortisolism result in the lack of hormone production that can lead to sudden death.Forensic pathologists in certain instances like encountering known cases of Addison's disease in which an unknown stress like superimposed disease or a stimulating event, has triggered a lethal adrenal crisis face the challenge to identify the precipitating event, which may be an infection or surgical procedure (27)

Pathologic findings at autopsy are a low combined weight and atrophy of adrenal glands making the adrenal glands difficult to detect. So, multiple slides of the fatty tissue surrounding the superior pole of each kidney should be taken for histologic examination. Microscopic appearance of adrenal gland tissue shows atrophy of adrenal cortical cells, and a collapsed vascular reticulin framework.Forensic pathologists may encounter cases of decedents with already known Addison's disease in which an unknown stress, such as superimposed disease or a stimulating event, has triggered a lethal adrenal crisis. The microscopic appearance of adrenal gland tissue shows atrophy of adrenal cortical cells, and a collapsed vascular reticulin framework In the past, tuberculosis was the most common cause of adrenocortical insufficiency and remains the primary cause in the developing countries where it accounts for about 20–30% of cases of Addison's disease.

Mycobacterium tuberculosis complex spreads to the adrenal glands hematogenously. Clinical manifestations may take 3 years to become apparent, and asymptomatic infection is also a common Case report of sudden death due to isolated adrenal tuberculosis.

Addison's disease has a relatively late onset. In most cases, adrenal TB is secondary to genitourinary TB or other pulmonary or extrapulmonary TB, or even more rarely primary due to reactivation of the disease.

ETIOLOGY:
Adrenal insufficiency is classified into primary or secondary (28)

Primary Adrenal Insufficiency:
Direct grievance to the adrenal cortex produces primary adrenal insufficiency (Addison disease).

Adrenal glands by autoimmune destruction cause of Addison disease.

Autoimmune adrenal disease patients are commonly have polyglandular autoimmune syndromes (29,30,30)

Type 1 autoimmune polyglandular syndrome is manifested by autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia, and consists of hypoparathyroidism, Addison disease, and candidiasis.

Type 2 autoimmune polyglandular syndrome encompass Autoimmune thyroiditis, Type 1 diabetes, pernicious anemia, vitiligo etc

Addison disease has been reported with celiac disease (31)

Infections include sepsis, tuberculosis, cytomegalovirus, and HIV (32)

The prevalence of tuberculosis has declined, but HIV has emerged as the most important cause of adrenal insufficiency associated with adrenal necrosis (33)

Bilateral adrenal hemorrhages can be precipitated by DIC, trauma, meningococcemia, neoplastic processes. An Adrenal crisis due to meningococcemia is known as the Waterhouse-Friderichsen syndrome (34)

Adrenal infiltration occurs in hemochromatosis, amyloidosis, and metastases.(35)

Ketoconazole inhibits adrenal enzymes.

Etomidate selectively inhibits 11β-hydroxylase, which converts deoxycortisol to cortisol.(36)

Secondary Adrenal Insufficiency:
Secondary insufficiency is due to unfamiliar steroid administration summing in the crushing of ACTH synthesis.(37)

- *Primary* = autoimmune-mediated intrinsic adrenal gland dysfunction (both cortisol and aldosterone deficiency).
- *Secondary* = chronic glucocorticoid administration resulting in hypothalamic-pituitary dysfunction (only cortisol deficiency).

Pathological consequences of infection:
Viruses:
Infection with the human immunodeficiency virus (HIV) predisposes individuals to numerous other infections, including viral diseases such as cytomegalovirus (CMV), that result in adrenal infection and dysfunction (38)

Studies have shown that as few as 26% of patients have correctly diagnosed antemortem CMV adrenalitis. One autopsy study of 128 patients with AIDS demonstrated that the adrenal gland was pathologically compromised in 99.2% of the subjects.(39)

However, direct destruction of the adrenal by HIVis unusual. In autopsy studies, the adrenal gland is the most commonly involved endocrine organ in patients with HIV. It Is estimated that adrenal insufficiency occurs in 5-8% of HIV infected individuals, which is substantially higher than the incidence in the general population. In addition to direct infection by HIV, AIDS patients revealed that CMV adrenalitis occurred in 56% and 48.4%, respectively. In individuals with AIDS, CMV is usually disseminated, but CMV adrenalitis may occur without clinical evidence of dissemination.CMV appears to cause a mixed inflammatory infiltrate with the cortex—medulla junction being the area of greatest injury, and the amount of necrosis in the region is directly correlated with the degree of direct CMV involvement.

Proposed etiologies for adrenal malfunction include opportunistic infections (i.e., CMV), AIDS-associated neoplasms (i.e., Kaposi sarcoma, non-Hodgkin's lymphoma), hemorrhage, viral-induced autoimmune destruction, and adverse effects of chemotherapeutics.(40)

Bacteria:
Bacteria affect the adrenal glands either by direct invasion of tissue or via secondary mediators.

The Waterhouse—Friderichsen syndrome is typically attributed to infection with Neisseria meningitidis, but it may occur in fulminant infections with other microbes, including smallpox. Streptococcus spp, Haemophilus influenzae, Corynebacterium diphtheriae, and Staphylococcus aureus,and able to experimentally induce adrenal hemorrhage in guinea pigs by injections of Bacillus anthracis, Clostridium tetani, Streptococcus spp and several Gram-negative bacilli.

Fungi:
Many pathogenic fungi are known to affect the adrenal glands. In endemic areas, pathogenic fungi can cause higher rates of adrenal insufficiency than any other infectious etiology.

H. capsulatum infection have been found to have an infected adrenal gland.(41)

It is postulated that the reason for the tropism of H. capsulatum for the gland is the local production and release of glucocorticoids and a relative lack of reticuloendothelial cells within the adrenal.

Destruction of the gland itself is thought to occur via direct infection by H. capsulatum leading to an extracapsular and intracapsular vasculitis causing local ischemia and caseation.(42)

Parasites:
Parasitic infections of the adrenal gland are rare occurrences with frequency rates dependent upon the organism, residence in endemic areas, and host immune integrity. Case reports have demonstrated adrenal involvement with such diverse pathogens as Microsporidia spp, amebic species Trypanosoma spp, Leishmania spp, and Echinococcus spp.(43)

The nature of involvement of the adrenal gland varies significantly depending on the microbe. Echinococcus spp cause hydatid disease, which presents with diffuse cystic involvement of visceral organs. The most commonly involved organs are the lungs and liver, with adrenal involvement representing 0.5% of studied cases, usually as part of a generalized infection and, more rarely, as primary cysts. It is estimated that hydatid disease accounts for 6—7% of all diagnosed cases of adrenal cysts.(44)

Diagnosis:
The best diagnostic tool to confirm adrenal insufficiency is the ACTH stimulation test however, if a patient is suspected to be experiencing an acute adrenal crisis, immediate treatment with IV corticosteroids is imperative and should not be delayed for any testing, as the patient's health can deteriorate rapidly and result in death without replacing the corticosteroids.

Dexamethasone should be used as the corticosteroid if the plan is to do the ACTH stimulation test at a later time as it is the only corticosteroid that will not affect the test results.

If not performed during crisis, then labs to be run should include: random cortisol, serum ACTH, aldosterone, renin, potassium and sodium. A CT of the adrenal glands can be used to check for structural abnormalities of the adrenal glands. An MRI of the pituitary can be used to check for structural abnormalities of the pituitary. However, in order to check the functionality of the Hypothalamic Pituitary Adrenal (HPA) Axis the entire axis must be tested by way of ACTH stimulation test, CRH stimulation test and perhaps an Insulin Tolerance Test (ITT). In order to check for Addison's Disease, the auto-immune type of primary adrenal insufficiency, labs should be drawn to check 21-hydroxylase autoantibodies.

Treatment:
Adrenal crisis:
Intravenous fluids, Intravenous steroid (injectable hydrocortisone) later hydrocortisone, prednisone or methylpredisolone tablets

Cortisol deficiency (primary and secondary)
Hydrocortisone, Prednisone, Prednisolone, Methylprednisolone, Dexamethasone,

Mineralocorticoid deficiency (low aldosterone)
Fludrocortisone acetate

CONCLUSION:
Addison disease is a life-threatening condition that requires accurate diagnosis and prompt treatment. If the diagnosis is delayed, it carries high morbidity and mortality. Inadequate secretion of the adrenocortical hormones may be primary from acquired disease of the adrenals (Addison's disease) or because of congenital deficiency of the enzymes required for the synthesis of adrenocortical hormones. It may be secondary to failure of ACTH secretion due to pituitary or hypothalamic disorders. Auto immune adrenal failure, and much less commonly, tuberculous destruction of the adrenals are the main causes of Addison's disease in the developed countries. In tuberculous destruction of adrenal there is caesation with giant cells, and calcification which may be detected radiologically in long standing cases.

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